Occupational pesticide exposure and the risk of death in patients with Parkinson's disease: an observational study in Southern Brazil.

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Research

Keywords: pesticides, Parkinson, mortality, occupational exposure, environmental exposure

Posted Date: March 5th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-16059/v1

Version of Record: A version of this preprint was published on June 17th, 2020. See the published version at https://doi.org/10.1186/s12940-020-00624-8.

Abstract

Background Multiple studies have suggested that various pesticides are associated with a higher risk of developing Parkinson's disease (PD) and may influence the progression of the disease. This study examines whether pesticide exposure influences the risk of mortality among patients with PD in Southern Brazil, when accounting for socioeconomic status, nicotine exposure, and caffeine exposure.

Methods 150 patients with idiopathic PD were enrolled from 2008-2013 and followed until 2019. In addition to undergoing a detailed neurologic evaluation, patients completed surveys regarding socioeconomic status and environmental exposures.

Results Twenty patients (13.3%) reported a history of occupational pesticide exposure with a median duration of exposure of 10 years (mean = 13.1, SD = 11.2). Patients with a history of occupational pesticide exposure had higher UPDRS-III scores, though there were no significant differences in regards to age, sex, disease duration, Charlson Comorbidity Index, and age at symptom onset. Patients with occupational pesticide exposure were more than twice as likely to die than their unexposed PD counterparts (HR = 2.32, 95% CI [1.15, 4.66], p = 0.22). Occupational pesticide exposure was also a significant predictor of death in a cox-proportional hazards model which included smoking and caffeine intake history and another which included several measures of socioeconomic status.

Conclusion In this prospective cohort study, we found an increased all-cause mortality risk in PD patients with occupational exposure to pesticides. More studies are needed to further analyze this topic with longer follow-up periods, more detailed exposure information, and more specific causes of mortality.

Background

The understanding of the etiology of Parkinson´s disease (PD) is still a work in progress. Although several genes have been implicated as monogenic causes of the disease, these are only responsible for approximately 10% of cases [1]. The remaining 90% of the cases are idiopathic, and different environmental exposures have been implicated as protective factors, such as tobacco smoking and caffeine intake, or risk factors such as heavy metals and pesticides [1].

Paraquat, a herbicide with molecular similarities to MPP+ (1-methyl-4-phenylpyridinium, a metabolite of the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)), was the first pesticide to be studied as a risk factor for PD. Soon after, other toxins such as rotenone and organophosphates were investigated with epidemiological evidence suggesting a higher risk of developing PD [2]. More recently, occupational exposure to a variety of pesticides including herbicides, insecticides, and fungicides were associated with the development of PD in France [3]. In addition to preferentially damaging dopaminergic neurons, these agents share several common mechanisms of action including increasing neuronal oxidating stress, damaging mitochondrial complex I, and impairing the ubiquitin-proteasome system [4, 5].

In addition to increased risk, data suggests that pesticides also anticipate age at onset [6], cause premature death in PD patients who are exposed to glyphosate [7] and can influence progression of motor, cognitive and psychiatric symptoms [4]. Considering this data, pesticides as a group may be involved in all stages of PD.

In previous investigations, we found that age at onset, chronological age, and non-white ethnicity were factors associated with higher all-cause mortality among PD patients [8]. However, in that analysis we were not able to examine the role of socio-economic or occupational factors. The role of occupational pesticides is particularly important to understand because, in recent years, the Brazilian government has approved swath of new pesticides, many of which contain substances that are illegal in the European Union. A record 450 new agrochemicals were approved in 2018, and based on data from the early months of this year, the new administration is on track to approve 480 new products within this year alone [9].

Considering that the use of these substances is projected to increase in the coming years, the objective of this prospective cohort study was to determine if pesticide exposure is associated with an increased risk of mortality among patients with PD in Southern Brazil, when accounting for socioeconomic status, nicotine exposure, and caffeine exposure. In particular, this study is focused on occupational pesticide exposure in settings such as agricultural work.

Methods

The data for this study is part of a larger cohort of 233 patients with idiopathic PD (as defined by the UK Parkinson Disease Brain Bank Diagnostic Criteria) who are followed at the Movement Disorders Clinic at Hospital de Clínicas de Porto Alegre (HCPA) and previously described [10]. The clinic is part of a tertiary health care system in Porto Alegre, a city in southern Brazil with a population of approximately 1.4 million. Ethics approval for this study was provided by Comitê de Ética em Pesquisa from HCPA. All patients or their next-of-kin provided verbal informed consent for participation in this study.

A subset of 150 patients completed questionnaires regarding environmental exposure history, and 126 patients completed an additional questionnaire regarding socioeconomic history. This data was collected during clinic visits, often with the help of a family member. The environmental exposure survey included information regarding occurrence and duration of occupational pesticide exposure, smoking history, alcohol use history, and caffeine intake. Since pesticide exposure is difficult to accurately quantify among the general population, we asked patients to report pesticide exposure in occupational settings, such as agriculture, landscaping, or pesticide production. The socioeconomic survey included information regarding employment history, average historical monthly income (when employed), insurance status, race, and education level. In addition to the survey information, each patient underwent neurologic evaluation (UPDRS and Hoehn & Yahr) by a neurologist trained in movement disorders. Charlson Comorbidity Index was used to assess the comorbidities of patients at baseline.

All statistical analysis was performed using R-Studio (Version 3.5.2). To determine survival time, clinic and hospital data was searched to determine whether patients were alive as of January 1, 2019. For

patients who were lost to follow up, national mortality databases were searched to identify confirmed deaths [11]. Patients who were lost to follow up, and without a confirmed date of death were right censored in the mortality analysis at the last known date of hospital admission or clinic follow up. For all survival analyses, age was used as the time scale rather than time-in-study due to ease of interpretability [12].

The primary analysis was a survival analysis testing (Kaplan-Meier curve with log-rank test; unadjusted hazard ratio) to compare PD patients who were exposed to occupational pesticides to those who were not. The secondary analyses sought to understand the impact of confounding of other environmental exposures and socioeconomic factors on the survival difference between the two cohorts. Because the number of individuals exposed to occupational pesticides in our sample was low, we examined the association between occupational exposure to pesticides and mortality adjusting for confounders through two separate multivariable cox proportional hazards models. The first cox proportional hazards model was adjusted to demographic and exposure-related factors and included any history of smoking, history of caffeine intake (80 mg or more per day, for at least 10 years), sex, and occupational pesticide exposure. The second cox proportional hazards model was adjusted to socio-economic factors and included sex, low historical income (< R$500/month), predominately agricultural employment, low education, private insurance coverage. Private health insurance coverage was used as a proxy of current wealth, since it is typically prohibitively expensive for the average Brazilian. In order to test the proportional hazards assumption for the survival analyses, the Schoenfield Residuals Test was applied to each model.

In order to test for a dose-response relationship between occupational pesticide exposure and risk of mortality, we performed an additional post-hoc cox proportional hazards model. Patients were divided into low exposure (< 10 years) and high exposure cohorts (≥ 10 years) based on the median duration of occupational pesticide exposure in this model.

Results

Of the 150 patients in this prospective cohort, 20 (13.3%) reported a history of occupational pesticide exposure. Females comprised 54% of the overall cohort. On average, patients were 64.4 years old (SD = 11.7) with 7.9 years of motor symptoms (SD = 5.2) at the time of study enrollment. 28.7% of patients had symptom onset prior to the age of 50 years. Twenty-two (14.7%) patients were lost to follow-up, after an average follow-up period of 8.9 years (SD = 2.5, median = 9.5 years). Sixty-two patients (41.3%) died prior to the final follow-up period (January 1, 2019), with a median age at death of 78 years (mean = 77.1, SD = 9.0).

Among the occupational pesticide exposure cohort, the median duration of exposure was 10 years (mean = 13.1, SD = 11.2). There were no differences between the occupational pesticide cohort and the control group in regard to age, sex, disease duration, Hoehn & Yahr score, medical comorbidities (according to the Charlson Comorbidity Index), and symptom onset [Table 1]. Pesticide exposure had a positive correlation

with total UPDRS motor score, and this association remained significant when controlling for disease duration [Additional File 1]. The average length of occupational pesticide exposure was 13.1 years (SD = 11.2, median = 10 years).

Table 1

Clinical and socioeconomic data from PD patients with and without occupational pesticide exposure.

Variable	All Patients	Occupational pesticide exposure?		p value[a]
		Yes	No	
Baseline characteristics	150	20	130	
Female sex	54%	45%	55.4%	0.53
Age at study enrollment (in years)	64.4 (11.7)	63.2 (11.7)	64.6 (11.8)	0.61
Lost to follow up	14.7%	10%	15.4%	0.77
Disease status				
Age at symptom onset	56.5 (12.1)	54.2 (10.9)	56.8 (12.3)	0.34
Disease duration at study onset	7.9 (5.2)	9.0 (6.6)	7.8 (5.0)	0.45
Symptom onset before 50 years	28.7%	45%	26.2%	0.14
Hoehn & Yahr Scale	2.5 (0.8)	2.7 (0.9)	2.5 (0.8)	0.36
Total UPDRS score	51.6 (23.5)	67.0 (28.9)	49.5 (22.0)	0.05
Levodopa equivalent daily dose, mg	855 (466)	931 (530)	843 (456)	0.49
Charlson Comorbidity Index	2.2 (1.3)	1.9 (1.1)	2.2 (1.3)	0.30
Exposure history				
Any smoking history	27.3%	30%	26.9%	0.79
Medium smoking history (10–30 pack-years)	9.3%	15%	8.5%	0.40
Heavy smoking history (> 30 pack years)	8.7%	5%	9.2%	1.0
Caffeine intake (at least 80 mg/day for 10 years)	61.3%	70%	60%	0.47
Socioeconomic status				
Patients in this subset	105	14	91	
Education (fewer than 9 years)	23.8%	22.2%	25%	1.0
Race (white)	91.4%	94.4%	91.7%	1.0

[a]For dichotomous variables, p-value obtained from $\chi 2$ testing, or Fisher's exact test for analyses with any values < 10. For continuous variables, p-value obtained from Welch's two sample t-test (two-tailed)

Variable	All Patients	Occupational pesticide exposure?		p value[a]
		Yes	No	
Private health insurance coverage	17.1%	14.3%	17.6%	1.0
Historical monthly income < minimum wage (when fully employed)	9.5%	0%	17.6%	0.12
History of working predominately in agriculture	9.5%	21.4%	7.7%	0.13

[a]For dichotomous variables, p-value obtained from $\chi 2$ testing, or Fisher's exact test for analyses with any values < 10. For continuous variables, p-value obtained from Welch's two sample t-test (two-tailed)

Socioeconomic information was available for a subset of 105 patients, including 14 patients with occupational pesticide exposure [Table 1]. Eleven (78.6%) patients who endorsed a history of occupational pesticide exposure reported predominately working in non-agricultural occupations for a majority of their working life. 17.6% of the control patients reported historically earning less than minimum wage when employed, compared to none of the patients with occupational pesticide exposure (p = 0.12). The pesticide exposure and control groups were similar in terms of race, private health insurance coverage, and educational attainment.

The survival curve of the occupational pesticide cohort was significantly different than the control group (log-rank test, p = 0.02). Patients with occupational pesticide exposure were more than two times as likely to die than their unexposed PD counterparts (HR = 2.32, 95% CI [1.15, 4.66], p = 0.22) [Figure 1]. Although the survival curves crossed during the survival analysis due to early censoring of multiple subjects in the occupational pesticides cohort, the Schoenfeld residual test indicated that the proportional hazards assumption was not violated.

Figure 2 displays the results of a cox proportional hazards regression that incorporated occupational pesticide exposure, sex, any smoking history, and caffeine intake history (at least 80 mg/day for 10 or more years). After adjusting for these exposure-related variables, occupational pesticide history was associated with a significantly elevated risk of mortality (HR = 2.29, 95% CI [1.13, 4.63], p = 0.02) [Figure 2]. A history of smoking, caffeine intake, and sex were not significant in this model.

In addition, the relationship between several socioeconomic variables, sex, occupational pesticide exposure, and mortality was examined in a separate analysis. Similar to the prior regression, patients who reported occupational pesticide exposure were at higher risk of mortality (HR = 3.92, 95% CI [1.41, 10.90], p = 0.009) [Figure 3]. None of the socioeconomic covariables (low historical income, predominately agricultural employment, low education, private insurance coverage) were significant in this regression analysis.

Finally, the post-hoc analysis in Table 2 demonstrates a dose-dependent relationship between occupational pesticide exposure and the risk of mortality. Patients with 10 or more years of occupational pesticide exposure had a significantly elevated risk of mortality (HR = 2.81, 95% CI [1.17, 6.73], p = 0.02), in contrast to patients with fewer than 10 years of exposure [Table 2].

Table 2
Post-hoc analysis for dose-dependent effect of occupational pesticide exposure.

Variable	Hazard Ratio	95% Confidence Interval	p Value
10 or more years of pesticide exposure	2.81	[1.17, 6.74]	0.02
Fewer than 10 years	1.84	[0.66, 5.17]	0.25

Discussion

This study was the first investigation performed in the low- and middle-income countries/Latin American/Brazilian context of the relationship between occupational pesticide exposure and PD mortality. The findings suggest that among a cohort of 150 patients with idiopathic PD in Southern Brazil, occupational pesticide exposure was associated with 2–4 times increased risk of all-cause mortality. This association was significant in the crude (unadjusted) analysis as well as in adjusted analyses controlling for other exposure-related factors and socioeconomic factors.

Pesticides are a broad class of chemical agents that are used to eliminate unwanted insects, animals, fungi, and plants. Although organochlorine insecticides are the most well studied neurotoxic pesticide [13], mounting evidence continues to support the link between other pesticides and the risk of developing PD. Literature points to a common mechanism of action through mitochondrial damage, and production of oxygen reactive agents, leading to DNA, lipid and protein damage, and impairment of the ubiquitin-proteasome system. This includes organophosphate insecticides, rotenone, pyrethroid insecticides, and certain herbicides (paraquat, maneb) [1, 13–16].

There appears to be a dose-response relationship between duration of pesticide exposure and PD risk (5 year exposure OR = 1.5, 95% CI: 1.02–1.09; 10 year exposure OR = 1.11, 95% CI: 1.05–1.18) [17]. In addition, high organophosphate exposure is associated with a faster progression of motor and cognitive symptoms during a 7.5-year follow up period [4]. The findings presented in the present study contribute to this evidence by demonstrating that the occupational pesticide exposure is associated with an increased risk of all-cause mortality among patients with PD. Furthermore, our dose-response analysis demonstrated that patients with 10 or more years of occupational pesticide exposure may have been driving the mortality difference in this study.

In the present study, the association between occupational exposure to pesticides and all-cause mortality among PD patients effect was significant even when controlling for socioeconomic contributors to lower life expectancy. Low educational attainment has been consistently linked to increased risk of death, with

a recent study suggesting the effect on mortality may be comparable to smoking [18, 19]. Similarly poverty is a well-cited risk factor for chronic disease and premature mortality both in Brazil and across the globe [20, 21]. When specifically comparing socioeconomic status and PD mortality, Yang et al. found that low-income was associated to higher mortality rates while Beard et al. identified higher rates in the high-income population [22, 23]. In our study, the mortality risk associated with occupational pesticide exposure was still observed when accounting for current wealth (as measured by private health insurance coverage), a history of low income, and low educational attainment. None of the patients in the occupational pesticide exposure cohort reported earning less than minimum wage, suggesting that low socioeconomic status is not the driver for the higher risk of mortality among patients with occupational pesticide exposure.

Given the inverse relationship between smoking and caffeine intake and the risk of developing PD, we sought to control for these factors in our analysis. Caffeine has a dose dependent effect reducing the risk of PD with a relative risk (RR) of 0.76 per 300 mg of caffeine (95% CI: [0.72–0.80]) [24]. This effect is seen especially in men [25] and includes different caffeinated beverages. Smoking also has a significant protective effect with a RR as low as 0.4 for a higher and longer history of intake [26]. In the present study, when controlling for these well-documented protective factors, occupational pesticide exposure remained statistically significantly associated with a 4-times higher hazard of mortality as compared to patients without occupational exposure to pesticides.

Interestingly, the majority of patients who reported occupational pesticide exposure did not report working predominately in agricultural jobs for the majority of their working life. In other words, since we only recorded the longest held occupation for each patient, most patients with fewer than 25 years of occupational pesticide exposure went on to work in other, non-agricultural professions for the majority of their working life. This suggests that a remote history of occupational pesticide exposure is associated with an increased risk of mortality in patients with PD, even among those who subsequently work in non-agricultural professions. Furthermore, the results from the multivariable cox proportional hazards model in Fig. 3 also support the notion that the pesticide exposure is truly driving this mortality difference, rather than other factors related to agricultural professions such as prolonged sun exposure or manual labor.

Unfortunately, the majority of patients in this study were unable to recall the specific agents that they were exposed to, limiting our ability to understand the potential variations in risk associated with different agrichemicals. Agricultural dependence on organophosphates and other pesticides continues to grow, creating an urgent need to better characterize the neurologic consequences of specific agents [13].

A notable limitation of this study is that we were unable to separate Parkinson-specific mortality from all-cause mortality due to the nature of the medical records and national obituary records. Therefore, our study was unable to conclusively determine if the link between pesticide exposure and mortality is truly due to faster progression of PD, even though we found that the motor UPDRS score was higher in the pesticide group when controlling for disease duration. Although it is possible that the increased risk of death is attributable to other exposure-related medical conditions, the baseline health status at the time

of enrollment was comparable between the two cohorts, as measured by the Charlson Comorbidity Index. This further supports our findings regarding the association between pesticide exposure and mortality risk.

Another limitation is the various enrollment dates (2008–2013) for the cohort, which could have induced time-based differences in the level of care received by the patients. However, statistical tests implemented to check for this possibility (Schoenfeld residuals of each of the univariable analyses and the multivariable cox proportional hazard regressions) were not significant, indicating that there was not a measurable time-related component to the variables used in this analysis. Because patients are of advanced age and were asked to report on occupational exposure throughout their lifetime, the possibility of recall bias cannot be excluded. However, because all patients interviewed had the same clinical condition and the questions about exposure were asked before the mortality outcomes were ascertained, we believe the possibility for recall bias is minimal.

Patients with more severe variants or rapid disease progression may not have been captured in this analysis. The time variable in the survival analysis was patient age rather than time from symptom onset in order to minimize the immortal time bias [27]. However, we acknowledge that this limits the interpretation of the survival times presented in this paper since patients were not enrolled at the time of symptom onset. Future studies would benefit from following patients from symptom onset or diagnosis in order to fully understand the impact of these socioeconomic and exposure related factors in a more prognostically meaningful way.

Conclusion

In this prospective cohort study, we found an increased all-cause mortality risk in PD patients with occupational exposure to pesticides. This risk was independent of sex, smoking, caffeine intake, and socioeconomic status, bringing more importance to our results. Even though the study does not account for specific pesticides, paraquat is still permitted in Brazil and glyphosate is widely used in many plantations including soybeans, which are one of the most important agricultural exports in the country. In this context of increasing prevalence of exposure by extremely toxic, recently approved new pesticides, this information is highly relevant. More studies are needed to further analyze this topic with longer follow-up periods, more detailed exposure information, and more specific causes of mortality. This is especially important in the Brazilian market, and perhaps in other developing countries, where new pesticides continue to be introduced without the corresponding research output necessary to understand the impact on human health [9].

Declarations

Ethics approval and consent to participate

Ethics approval for this study was provided by Comitê de Ética em Pesquisa from HCPA. All patients or their next-of-kin provided verbal informed consent for participation in this study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest to disclose.

Funding

Fundo de Incentivo à Pesquisa (FIPE-HCPA).

Author´s contributions

MSM contributed with data collection, analysis and manuscript elaboration. SPR analyzed the data and was a major contributor in writing the manuscript. MPS had an important role in writing the manuscript. AFSS and CRMR helped with the study concept and were important to interpret the results and to revise the final manuscript.

Acknowledgements

Not applicable

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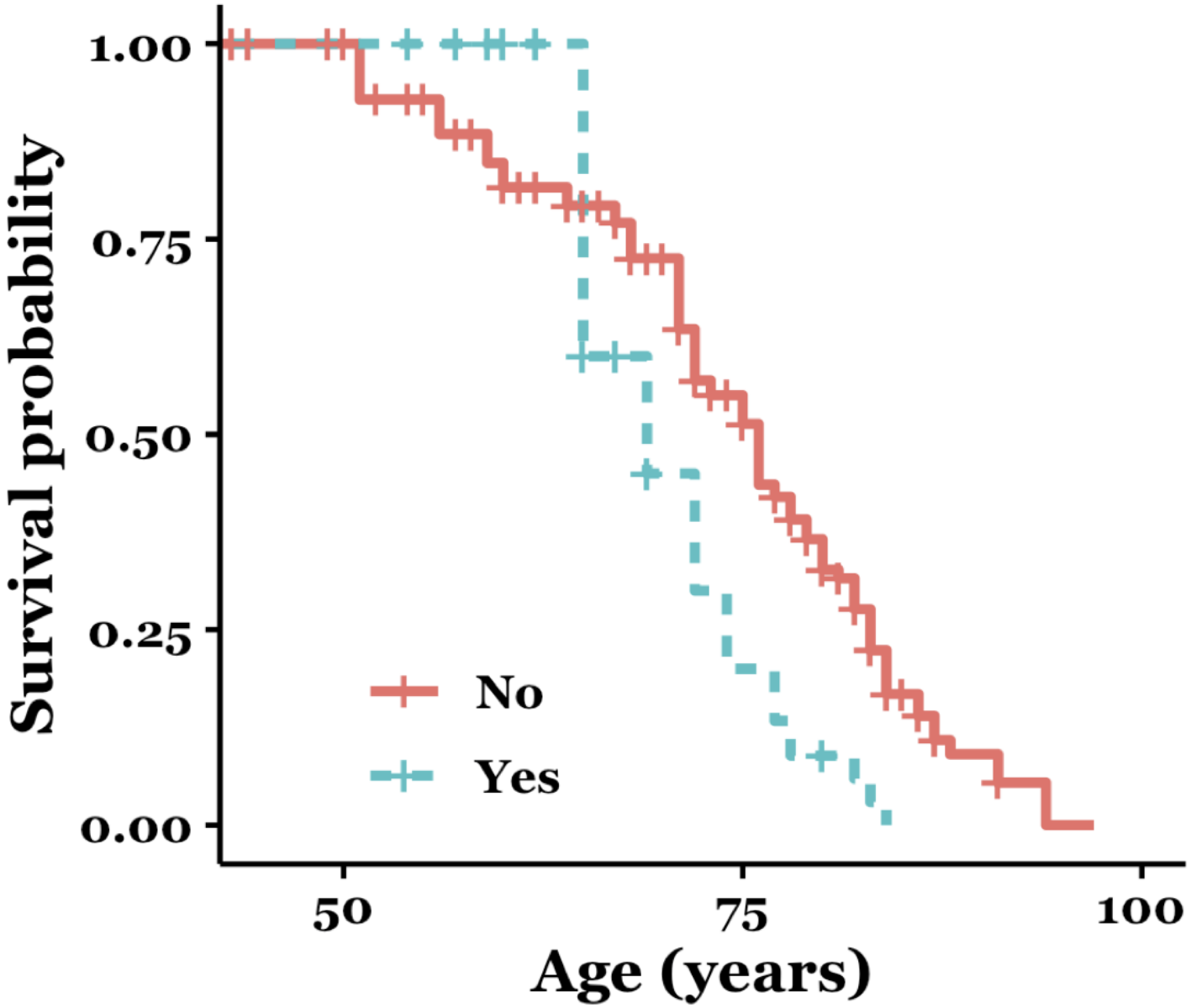
Figures



Variable	HR	95% CI	p-value
Occupational pesticide exposure	2.32	[1.15, 4.66]	0.018

Figure 1

Survival curve comparing patients with and without self-reported occupational pesticide exposure (n = 150, p-value from log-rank test)

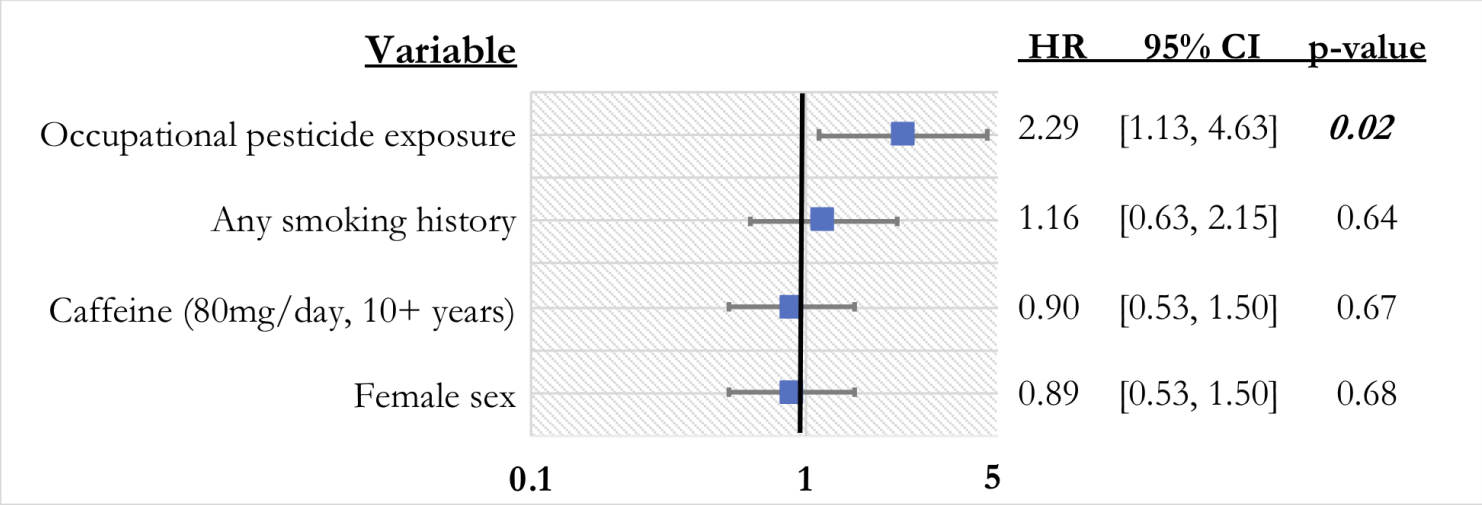


Figure 2

Impact of occupational pesticide exposure on mortality when controlling for smoking, caffeine intake, sex, and age (Multivariable cox proportional hazards model; n = 150, concordance = 0.60, SE = 0.04. Global Schoenfeld residual is p > 0.05))

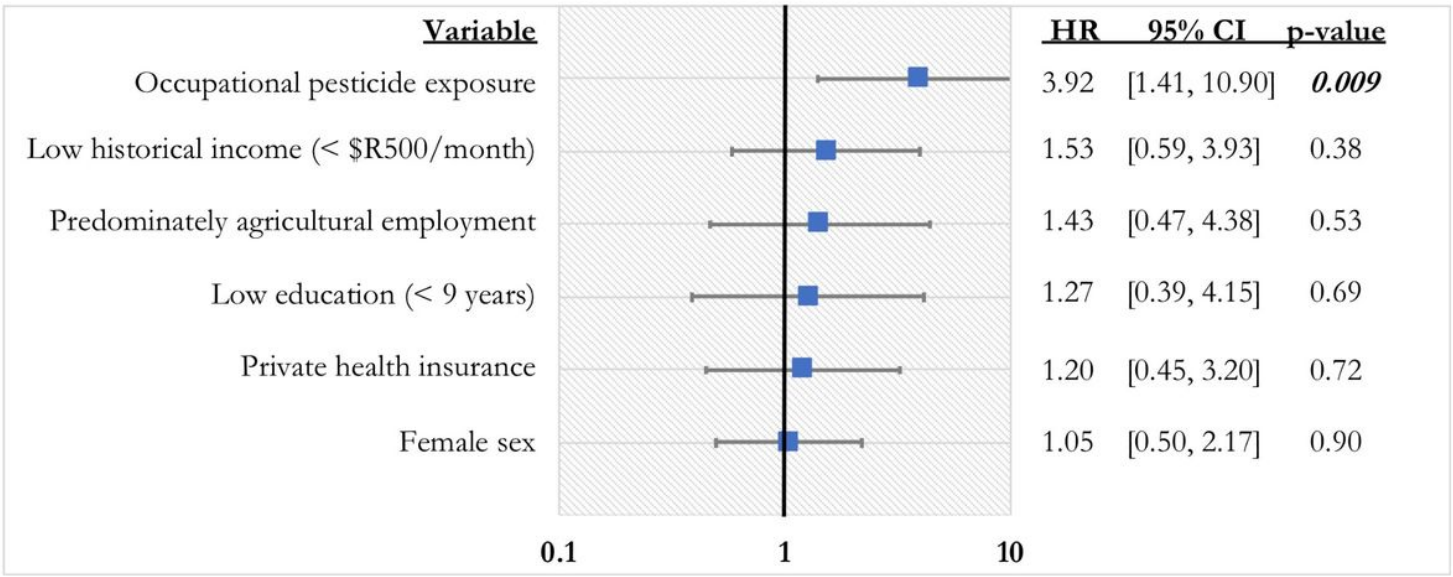


Figure 3

Impact of occupational pesticide exposure on mortality when controlling for sex, age, and socioeconomic status (Multivariable cox proportional hazards model; n = 105, concordance = 0.60, se = 0.06 Global Schoenfeld residual is p > 0.05))

Supplementary Files

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